

with oral contraceptives. Without being able categorically to deny this possibility I think it unlikely for the following reasons.

Retinol in human blood is predominantly bound to a specific transport-protein known as the retinol-binding protein (RBP). Under physiological conditions RBP binds to pre-albumin.⁴ The amount of free retinol is very small indeed. Using a fluorescence assay⁵ measurements have been made of the amount of RBP in plasma from 10 women before starting to take a combined oral contraceptive (Minovlar: 1 mg norethisterone acetate and 50 µg ethynylestradiol) and again after three months' treatment. The mean pretreatment level of RBP was 42±8 (S.D.) µg/ml, but this rose to 75±10 µg/ml during treatment.

This finding indicates that the rise in serum vitamin A level during the taking of oral contraceptives is due to an increased concentration of RBP. The amount of free retinol is unchanged. Hypervitaminosis A and the teratogenic effects of the vitamin in pregnant animals are seen with doses which far exceed the binding capacity of RBP. It seems unlikely that an increase in protein-bound retinol is hazardous. A very analogous situation occurs with corticosteroids, where plasma levels are very high in women taking oral contraceptives owing to an increase in transcortin.⁶

The increase in plasma RBP seen in women taking oral contraceptives is probably due to the oestrogen component, for plasma retinol is not increased by progestogens alone.² Serum vitamin A is also raised in volunteers exposed to DDT,⁷ for this compound yields oestrogenic metabolites.—I am, etc.,

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Effect of Natural Oestrogens on Coagulation

SIR,—A recent leading article (9 February, p. 213) concluded that the oestrogen component of the oral contraceptive is the agent responsible for the thrombotic episodes associated with the taking of steroid contraceptives. It was further stated that the untoward effect was probably due to the nature of the oestrogen used and that substitution with a natural oestrogen might avoid the problem of thrombosis altogether.

We have recently completed a study which has shown that natural oestrogens (Premarin) when administered to postmenopausal women for a period of one year had no adverse effect on their coagulation mechanism.

The subjects were 30 postmenopausal patients (mean age 50.53 years) attending the climacteric clinic at Addington Hospital, Durban. Baseline observations were taken for the assessment of the following coagulation factors: fibrinogen, platelet count, single

Mean Coagulation Values (±S.E.M.) in 30 Postmenopausal Women, Before, During, and After Treatment with Natural Oestrogen

Test	Baseline:	After 3/12 treatment	After 9/12 treatment	1/12 after stopping treatment
Fibrinogen (mg/100 ml)	360.8 ± 17.8	300.5 ± 10.7	325.6 ± 12.2	371.0 ± 13.1
Platelets (/mm ³)	281,500 ± 17,100	231,700 ± 12,100	203,800 ± 14,700	222,600 ± 14,100
Factor V (%)	109.9 ± 5.0	103.2 ± 5.5	102.0 ± 4.1	108.2 ± 4.5
Factor X (%)	114.5 ± 4.9	112.6 ± 4.0	117.4 ± 6.0	112.2 ± 4.9
S.S.P.T. (sec.)	12.23 ± 0.11	12.19 ± 0.11	12.37 ± 0.10	12.12 ± 0.13
K.P.T.T. (sec.)	43.97 ± 0.97	45.99 ± 0.88	45.56 ± 0.89	50.40 ± 1.15

stage prothrombin time (S.S.P.T.), kaolin partial thromboplastin time (K.P.T.T.), factor V and X assays, and euglobulinolysis time. Standard haematological techniques were employed.¹ The patients were then started on treatment (Premarin 1.25 mg daily, given cyclically for three weeks at a time) and the tests repeated at the end of three months and nine months. At the end of a year's treatment medication was suspended for a month and the tests repeated.

The results are shown in the table. The only statistically significant feature was a progressive fall in the platelet count (P = <0.05, <0.01, and <0.02 after three months' and nine months' treatment and one month after stopping treatment respectively).

The natural oestrogens had no effect on the "dynamic" tests of coagulation. The values for the S.S.P.T. and K.P.T.T. in our patients were similar to those in normal controls tested at the same time. Though factor X has been reported to be increased in women on prolonged treatment with oral contraceptives,² no change in this parameter was noted in the present study. This may be of considerable importance in view of the possible key role of this factor in thrombogenesis.³ Fibrinolysis was similarly unaffected by treatment with the natural oestrogens as the euglobulinolysis time remained consistently greater than two hours throughout the series.

This is a preliminary report on the first documented prospective investigation of the long-term effect of natural oestrogens on coagulation. Though the significance of the depressant effect of these steroids on the platelet count is not known, it may be concluded that treatment of a group of menopausal women with natural oestrogens for one year had no adverse effect on their coagulation mechanism. As suggested in your leading article, it might well be that the substitution of a natural oestrogen would in fact avoid the problem of thrombosis associated with oral contraception.—We are, etc.,

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The Coroners' So-called 24-hour Rule

SIR,—Dr. J. F. Heggie (22 June, p. 667) has quoted the Human Tissue Act 1961 section

2(1) as giving clear permission for post-mortem examination to be carried out on any patient dying within 24 hours in hospital.

However, the provisions of the Coroners Act 1887, Coroners Amendment Act 1926, and the Coroners' Rules 1953, together with regulations and statutory instruments thereunder, establish coroners' practice, which is that there is a legal obligation upon the coroner to inquire into all sudden and unexpected deaths or deaths of which the cause is unknown.

The Human Tissue Act provision is permissive; the law relating to coroners is obligatory. The so-called "24-hour rule" is merely a rough guide; the doctor is obliged by common law to report all sudden and unexpected deaths and deaths the cause of which are unknown to the coroner, irrespective of any "rule." The coroner has the right to appoint any pathologist of his choosing to conduct any post-mortem examination, irrespective of the Human Tissue Act. All these matters (and many others) were dealt with at length in the Brodrick Report.¹—I am, etc.,

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¹ Home Office. *Report of the Committee on Death Certification and Coroners*, Cmnd. 4810. London, H.M.S.O., 1971.

Maternal Blood Group A and Pre-eclampsia

SIR,—Mr. D. P. L. May (22 December 1973, p. 738) has reported a preponderance of blood group A among patients with pre-eclampsia. His finding could support the intravascular coagulation hypothesis¹ of the aetiology of toxæmia since it parallels the observations that group A subjects tend to be more at risk for venous thromboembolic disease associated with pregnancy and use of oral contraceptives,² as well as for coronary artery thrombosis.³

We have measured the frequency of eclampsia and pre-eclampsia, as recorded in labour ward books, among 10,180 women delivering in West Jerusalem's four hospitals in 1965-9 for whom blood group data were available. These blood group data were added to a sample⁴ of the computer-stored files in the ongoing Jerusalem Perinatal Study.⁵ There was no excess of toxæmia recorded among group A mothers, but there was an apparent interaction between rhesus and 0 types, with 0+ mothers having fewer and 0- mothers more cases of toxæmia than expected (table I). Apart from the excess recorded in 0- women, these differences in toxæmia

rates might have been expected on the basis of the distribution of maternal age, parity, and ethnic group in mothers of different blood groups in the Jerusalem population.

TABLE I—Recorded Frequency of Toxaemia by Blood Groups

Blood Group	No. of Births	Pre-eclampsia (%)
Rh + A	3,696	1.70
B	2,101	1.91
AB	866	1.75
O	3,431	1.14*
Rh - A	388	0.59
B	250	2.40
AB	85	—
O	363	3.03*
Total	11,180	1.58

In an earlier case-control study⁶ in which patients with toxaemia, defined by standard criteria, were matched with mothers of similar age, parity, and ethnic group there were no significant blood group differences between patients and controls (table II). Nor did the few cases of frank eclampsia show any unusual blood-group distribution. We are therefore unable to confirm any association between toxaemia and blood group A.

TABLE II—Blood Group Distribution of Patients with Eclampsia and Pre-eclampsia and Controls

Blood Group	Patients	Controls
Rh + A	39	38
B	16	25
AB	5	7
O	45	40
Rh - A	5	4
B	3	2
AB	1	0
O	0	1
Unknown	7	4
Total	121	121

It is not unlikely that in Britain, too, women of different blood groups differ in respect of ethnic background, social class, age, parity, and religion. Women delivered in particular hospitals may also provide a very biased population sample. Since the distribution of these variables affects the incidence of pre-eclampsia it would be important to take them into account in studying the relationship of the disease to blood groups.—We are, etc.,

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Coxsackie Viruses and Diabetes Mellitus

SIR,—Dr. D. R. Gamble and his colleagues (3 November 1973, p. 260) have presented evidence associating infection with Coxsackie B4 virus and the onset of insulin-dependent

Admission and Convalescent Antibody Titres Shown Side by Side for Coxsackie B1—B5 and Mumps

Case No.	Age (Yrs)	Sex	Month of Presentation	Coxsackie B1	Coxsackie B2	Coxsackie B3	Coxsackie B4	Coxsackie B5	Mumps
1	13	M	January	— —	— —	— —	— —	— —	— —
2	5	M	January	— —	— —	— —	— —	— —	— —
3	5	M	February	— —	— —	— —	— —	— —	— —
4	6	F	July	— —	— —	— —	— —	— —	— —
5	12	F	August	— —	— —	— —	— —	— —	— —
6	5	F	September	— —	— —	— —	— —	— —	1/4 1/16
7	9	M	October	— —	— —	— —	— —	— —	— —
8	11	F	October	— —	— —	1/64 1/64	— —	— —	— —
9	11	M	November	— —	— —	— —	— —	— —	1/16 1/16
10	13	M	December	— —	1/64 1/64	1/16 1/16	— —	— —	— —
11	7	F	December	— —	1/16 1/16	— —	— —	— —	— —

diabetes in young adults. However, as they point out, among the patients aged 9 years or less there was no significant difference in the incidence of neutralizing antibodies to Coxsackie type B4 when compared with a control group of normal children. They suggest that other viruses may possibly initiate diabetes in childhood.

We have looked for evidence of recent virus infection in 11 children who presented with diabetes over the past year. The mean duration of symptoms for this group of patients was seven weeks; no child had a history suggestive of a premonitory illness in the preceding three months. Sera were taken for virological studies at the time of the acute admission and subsequently at an outpatient visit. The mean time interval between the two samples was 6.8 weeks. The age, sex, and month of presentation of the cases are shown in the table, together with the results of the tests for neutralizing antibodies to Coxsackie B group viruses 1-5 and complement fixing antibodies to mumps.

The sera were screened at a dilution of 1/16 for the Coxsackie B group antibodies and any positive at this titre was titrated. Eight of the patients were negative at this dilution. Cases 10 and 11 had a titre of 1/16 or greater for Coxsackie B2 and cases 8 and 10 for Coxsackie B3, but in no child was there a rise in titre to support a diagnosis of recent infection.

In one of the two cases with demonstrable mumps antibodies (case 6) there was a rise in the S antibody titre indicative of very recent mumps. This might be considered a normal occurrence among a group of 11 children.

No significant titre or four-fold or greater rise in titre was found in complement fixation tests for Q fever, psittacosis/ornithosis, *Mycoplasma pneumoniae*, influenza A or B, parainfluenza, or infection with adenoviruses, respiratory syncytial virus, cytomegalovirus, herpes simplex, and varicella. Most children had a high titre of antibody to measles virus, as might be expected at their age.

Tissue cultures were inoculated with throat swab extracts from seven children; and tissue cultures and newborn mice with stool specimens from four children, collected when the children were first admitted to hospital. A rhinovirus was isolated from one child and adenovirus type 7 from the stool of the same child; all other specimens were negative on tissue culture and in mice.

We conclude from these observations that Coxsackie B4 virus played no aetiological role in diabetes in these 11 children and none of the other agents or viruses in eight of them. It is not possible to state categorically whether or not Coxsackie B viruses 2 or 3 in three cases or mumps virus in two cases may have damaged the pancreas.

We wish to thank the staff of the Virology

Laboratory, Radcliffe Infirmary, for their great assistance with this study.—We are, etc.,

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Confusion of Tongues

SIR,—The Duke of Cumberland referred to the Highland clansmen as speaking "with their Irish tongues," a comment which has no doubt endeared him even less to the descendants of those slain at Culloden. Drs. P. A. Emerson and M. S. Lewis (1 June, p. 488) refer to the language of Northern Belgium as Dutch. Sir, the language of Northern Belgium is Flemish. Such is the friendship and courtesy of our colleagues in Ghent and Antwerp, and moreover their realization of the linguistic incompetence of the British, that they would be ready again to welcome Drs. Emerson and Lewis as they have done before. Nevertheless I think an apology to them for the error would not be out of place.—I am, etc.,

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The Killer Worm

SIR,—Tetanus unfortunately is all too common in India, up to 30 or 50% of cases proving fatal. Even more prevalent is the intestinal nematode *Ascaris lumbricoides*. That there could be any connexion between the presence of ascaris in the bowel and the outcome in a case of tetanus may at first seem unlikely. However, our observation has been that a severe or fatal laryngeal spasm in tetanus often directly precedes the passage of a roundworm from the nose or mouth. The worm presumably stimulates vagal afferent fibres in the pharyngeal mucosa in the neighbourhood of the epiglottis which initiates reflex spasm of the laryngeal muscles. A true cough is seldom possible in severe tetanus because of the rigidity of the muscles involved in the reflex.

What encourages the worm to migrate upwards from its position in the bowel is open to speculation. The constantly high intrathoracic and abdominal pressures caused by muscle contraction could interfere with oxygen entry into the bowel and create an environment unfavourable to the worm.¹ Escape downwards would prove difficult in the tetanus patient, who is frequently constipated. Another factor to be considered is that we give these patients chlorpromazine in